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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/656,358 | 09/04/2003 | Donna L. Robinson | S-100,543 | 8708 |

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| EXAMINER | |
|---|---|
| PANARO, NICHOLAS J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 11/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/656,358 | ROBINSON, DONNA L. | |
| | Examiner | Art Unit | |
| | Nicholas J. Panaro | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Drawings*

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

### *Claim Objections*

Claim 1 is objected to because of the following informalities: Regarding Claim 1, two steps are labeled as "step (e)". The second step (e) should be labeled step (g). Appropriate correction is required.

Claim 5 is objected to because of the following informalities: the word "the" is repeated. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

The term "dissociation temperature (Td)" as defined by the inventor in the specification refers to the temperature at which a polynucleotide, oligonucleotide or primer will become functionally dissociated from a complementary strand to which it is or may be bound or annealed (Page 14, Lines 8-10). Regarding Claim 1(a)(ii), the inventor claims a primer set wherein the Td of the primers in the primer set are between about 72°C and 75°C. Regarding Claim 1(d), the inventor claims primer extension is achieved at a temperature of between about 75°C and 78°C for between about 3 to 4 minutes. Using the definition of dissociation temperature as stated by the inventor, the primer set claimed in Claim 1(a)(ii) would become "functionally dissociated" from the sample DNA between about 72°C and 75°C. Thus, the primer set of Claim 1(a)(ii) would functionally dissociate from the sample DNA at a temperature of about 75°C to 78°C and DNA extension could not take place as stated in Claim 1(d). Claims 2-9 are rejected as being dependent upon a rejected claim.

Breadth of the Claims

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. The claims as written are broad with respect to what is claimed. The specification states that the dissociation temperatures of the primer set are between about 72°C and 75°C and the extension temperature is between about 75°C and 78°C. Enablement may occur wherein the dissociation temperature and the extension temperature are both about 75C. However, when the Td is less than 75°C (e.g., 72°C) and the extension temperature is above 75°C (e.g., 78°C) the primer set should become

functionally dissociated from the sample DNA and the extension of DNA will become impossible. Therefore, while the specification may be enabling at 75°C, the specification is not enabling for the broadly claimed invention.

Nature of the Invention

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. Extension requires that the primer set be hybridized to the sample DNA (U.S. Patent 4,965,188, Column 11, Lines 50-61; Column 12, Lines 11-12, 37-39 and 48-50). However, the nature of the invention claimed is such that the extension temperature is greater than the dissociation temperature of the primers. The specification states that the dissociation temperatures of the primer set are between about 72°C and 75°C and the extension temperature is between about 75°C and 78°C. Enablement may occur wherein the dissociation temperature and the extension temperature are both 75°C. However, when the Td is less than 75°C (e.g., 72°C) and the extension temperature is above 75°C (e.g., 78°C) the primer set should become functionally dissociated from the sample DNA and the extension of DNA will become impossible. Therefore, while the specification may be enabling at 75°C, the specification is not enabling for the broadly claimed invention.

The method requires primer extension and the nature of primer extension is such that primers must be annealed to be extended (U.S. Patent 4,965,188, Column 11, Lines 50-61; Column 12, Lines 11-12, 37-39 and 48-50). However, the instant claims require primer extension at temperatures greater than Td. This appears to contradict the nature of primer extension.

State of the Prior Art

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. The prior art does not teach successful amplification of DNA via the polymerase chain reaction wherein the extension temperature is greater than the dissociation temperature (U.S. Patent 4,965,188, Column 11, Lines 50-61; Column 12, Lines 11-12, 37-39 and 48-50). The specification states that the dissociation

temperatures of the primer set are between about 72°C and 75°C and the extension temperature is between about 75°C and 78°C. Enablement may occur wherein the dissociation temperature and the extension temperature are both 75°C. However, when the Td is less than 75°C (e.g., 72°C) and the extension temperature is above 75°C (e.g., 78°C) the primer set should become functionally dissociated from the sample DNA and the extension of DNA (use "primers" instead of DNA here?) will become impossible. Therefore, while the specification may be enabling at 75°C, the specification is not enabling for the broadly claimed invention.

Level of Predictability in the Art

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. The level of predictability in the art is very low because the prior art does not teach successful amplification of DNA via the polymerase chain reaction wherein the extension temperature is greater than the dissociation temperature (U.S. Patent 4,965,188, Column 11, Lines 50-61; Column 12, Lines 11-12, 37-39 and 48-50). The specification states that the dissociation temperatures of the primer set are between about 72°C and 75°C and the extension temperature is between about 75°C and 78°C. Enablement may occur wherein the dissociation temperature and the extension temperature are both 75°C. However, when the Td is less than 75°C (e.g., 72°C) and the extension temperature is above 75°C (e.g., 78°C) the primer set should become functionally dissociated from the sample DNA and the extension of DNA (use "primers" instead of DNA here?) will become impossible. Therefore, the level of predictability in the art is very low with regard to successful amplification of DNA via the polymerase chain reaction wherein the extension temperature is greater than the dissociation temperature.

Existence of Working Examples

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. The working examples present in the specification use a forward primer with a Td = 74.2°C (SEQ ID NO: 1) and a reverse primer with a Td = 73.4°C (SEQ ID NO: 2) and 60 cycles of amplification wherein the

extension temperature is 75°C. In contrast, Example 3 uses the same primers and an extension temperature of 65°C which is not within the claimed temperature range (Figure 4). The specification provides Examples 2 and 3 using primers with Td of 73.4°C and 74.2°C. Example 2 illustrates extension at 75°C while in contrast Example 3 illustrates extension at 65°C. The extension of Example 3 is not within the claimed range. Hence, the only working example of the claimed invention is Example 2. As stated above, the claims are drawn to a wide range of Td and extension temperatures. Those illustrated in Example 2 represent a very small window when the primer would not be functionally dissociated as defined by the instant specification. Hence, the primers of the working examples would become "functionally dissociated" from the sample DNA at 74.2°C and 73.4°C, respectively (i.e, below the extension temperature). Thus, DNA extension and incorporation of fluorescently-labeled ddNTPs into the amplicon would not be possible. Therefore, the specification does not provide working examples of the broad temperature ranges of claimed invention which would enable one of ordinary skill in the art to make and use the invention as claimed.

Quantity of Experimentation Required

The claims are drawn to a method of fluorescence-based cycle sequencing of a DNA sample. In view of the breadth of claims being drawn to a method of fluorescence-based cycle sequencing of a DNA sample; in view of the nature of the invention in which the extension temperature is greater than the dissociation temperature of the primers; in view of the state of the prior art which does not teach successful amplification of DNA via the polymerase chain reaction wherein the extension temperature is greater than the dissociation temperature; in view of the level of unpredictability in the art with regard to successful amplification of DNA via the polymerase chain reaction wherein the extension temperature is greater than the dissociation temperature; in view of the lack of working examples of the broadly claimed invention, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

**Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Td of between about 65°C and 75°C, does not reasonably provide enablement for a Td of between about 57°C and 65°C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.**

The claim is drawn to a method of fluorescence-based cycle sequencing of a DNA sample. As stated above, extension requires that the primer set be hybridized to the sample DNA (U.S. Patent 4,965,188, Column 11, Lines 50-61; Column 12, Lines 11-12, 37-39 and 48-50). However, the nature of the invention claimed is such that the extension temperature is greater than the dissociation temperature of the primers. The claim states that the dissociation temperatures of the primer set are between about 57°C and 75°C and the extension temperature is 65°C. Enablement may occur wherein the dissociation temperature is greater than the extension temperature (i.e., wherein Td > 65°C). However, when the Td is less than 65°C (e.g., 57°C) and the extension temperature is 65°C the primer set should become functionally dissociated from the sample DNA and the extension of DNA will become impossible. Therefore, while the specification may be enabling wherein Td > 65°C, the specification is not enabling for the broadly claimed invention (i.e., wherein Td < 65°C).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 1-9 are indefinite in Claim 1 for the following reasons: indefinite in step (b) for "the DNA" because it is unclear whether it refers to "sample DNA" or "DNA primers" or some other DNA; indefinite in step (e) because "the reaction mixture" lacks antecedent basis in the preceding steps; indefinite in step (e)[g] because "the series" lacks antecedent basis in the preceding steps; indefinite for the repeated phrase "at least about".**

It is vague and indefinite what is meant by the phrase "at least about 3 minutes". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that the values above and below 3 minutes are permitted. Further, the extent of variance permitted by "about" is unclear in this context.

Similarly, it is vague and indefinite what is meant by the phrase "at least about 30 seconds". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that the values above and below 30 seconds are permitted. Further, the extent of variance permitted by "about" is unclear in this context.

In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their Specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

***Conclusion***

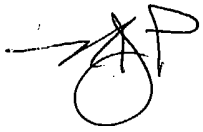
Claims 1-10 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicholas J. Panaro whose telephone number is (571) 272-0778. The examiner can normally be reached on Monday - Friday 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NJP



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